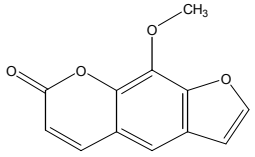
METHOXSALEN WITH ULTRAVIOLET A THERAPY (PUVA)*

First Listed in the *Fourth Annual Report on Carcinogens*



CARCINOGENICITY

Methoxsalen (methoxypsoralen) (CAS No. 298-81-7) with ultraviolet A (long-wave) therapy (PUVA) is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans (IARC S.4, 1982; IARC S.7, 1987). The development of basal cell and squamous cell skin cancers has been reported in patients treated with methoxsalen and long-wave ultraviolet light. Three cases of malignant melanoma of the skin have been reported in patients with psoriasis treated with PUVA. The strongest evidence for a casual association between PUVA treatment and nonmelanocytic skin cancer comes from the follow-up study of 1,380 psoriatic patients. The standardized incidence ratio (SIR) for squamous cell carcinoma increased from 4.1 (95% confidence interval, 2.3-6.8) at low doses to 22.3 (13.5-34.1) at medium doses and 56.8 (42.7-74.2) at high doses; this effect was independent of possible confounding effects of therapy with ionizing radiation and topical tar. The effect on basal cell cancer incidence was much weaker (high doses: SIR, 4.5; 2.8-6.9). One cohort study of 525 psoriatic patients treated with PUVA did not suggest an increase in the incidence of skin cancer (mean follow-up period, 2.1 years), but this "negative" result could have been due to lack of statistical power and to the low doses used in the study. Another study with 5-year follow up showed no skin tumor in 94 patients treated with PUVA. Methoxsalen alone did not alter the incidence of skin cancer over 2 years in two small controlled trials of its use (IARC V.24, 1980; IARC S.4, 1982).

An IARC Working Group reported that there is sufficient evidence of carcinogenicity of Methoxsalen (methoxypsoralen) (CAS No. 298-81-7) with ultraviolet A (long-wave) therapy (PUVA) in experimental animals (IARC V.24, 1980; IARC S.4, 1982; IARC S.7, 1987). When administered topically, methoxsalen plus exposure to ultraviolet light induced skin tumors, primarily epidermal papillomas and carcinomas, squamous cell carcinomas, fibrosarcomas, and basal cell tumors, in mice. Some squamous cell and basal cell carcinomas metastasized. When injected intraperitoneally with methoxsalen and exposed to ultraviolet irradiation, female mice developed increased incidences of epidermal fibrosarcomas and squamous carcinomas of the ears and eye region and epidermal papillomas and carcinomas of the ears (IARC V.24, 1980; IARC S.4, 1982).

PROPERTIES

Methoxsalen occurs as white-to-cream-colored, odorless, fluffy, needle-like crystals. It is soluble in boiling ethanol, acetone, acetic acid, propylene glycol, benzene, vegetable oils, and chloroform; practically insoluble in cold water; and sparingly soluble in boiling water and

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* There is no separate CAS Registry Number assigned to methoxsalen (methoxypsoralen) with ultraviolet A (PUVA).

commercially as a grade containing 98%-102% active ingredient. Possible impurities include ammidin and bergapten. When heated to decomposition, methoxsalen emits acrid smoke and fumes.

USE

Methoxsalen is used mainly in combination with sunlight or long-wave (320-400 nm) ultraviolet light in the treatment of vitiligo and severe psoriasis. Methoxsalen is also used to increase skin tolerance to sunlight (IARC V.24, 1980) as a sunburn protector and a suntan accelerator (HSDB, 1997).

PRODUCTION

Current production data on methoxsalen are not available. The 1998 Chemical Buyers Directory lists three U.S. suppliers of the chemical, and Chemcyclopedia 98 names one supplier (Tilton, 1997; Rodnan, 1997). In 1980, there was one producer of methoxsalen in the United States, but no data were available on the amount produced (IARC V.24, 1980).

EXPOSURE

The primary routes of potential human exposure to methoxsalen are dermal contact and ingestion. Methoxsalen rapidly penetrates into the epidermis and dermis when it comes into contact with the skin. Both oral and topical administration require subsequent exposure to sunlight or ultraviolet light for medicinal effectiveness. Oral dosage is 20 to 50 mg, no more than every other day. When applied topically, a 0.1%-0.15% solution is used for psoriasis treatment, and a 1.0% solution is used for vitiligo treatment. Methoxsalen treatment is usually followed within 2 to 4 hr by a 5-min. exposure to sunlight or long-wave (320-400 nm) ultraviolet light. Exposure to light may be gradually increased to 30 min. FDA requires that the pharmaceutical product be labeled with a warning regarding a ninefold increased risk of squamous cell carcinoma among PUVA-treated patients. Potential occupational exposure to methoxsalen may occur during preparation, formulation, administration or application of the pharmaceutical. Occupational exposure to ultraviolet light may also occur during therapy. Methoxsalen is a naturally occurring substance which is produced by several plants and a fungus (IARC V.24, 1980).

REGULATIONS

FDA regulates methoxsalen as a prescription drug approved for human use under the Food, Drug, and Cosmetic Act (FD&CA). NIOSH recommends that exposure to ultraviolet light of wavelength 315-400 nm not exceed 1.0 mW/cm^2 for > 1,000 seconds, and 1 J/cm^2 for exposure $\leq$ 1,000 seconds. OSHA regulates methoxsalen with ultraviolet A radiation under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table A-29.